IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.'S DOCKET: KORSGREN-1

In re Application of:	)	Conf. No.: 9165
Olle KORSGREN et al.	)	Art Unit: 1614
Appln. No.: 09/890,936	)	Examiner: Donna A. Jagoe
Filed: November 7, 2001	)	Washington, D.C.
For: NOVEL USE WITH TRANSPLANTATION SURGERY	)	August 15, 2008

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Randolph Building, Mail Stop AF
401 Dulany Street
Alexandria, VA 22314

Sir:

The present invention, as recited in independent claims 4 and 27, relates to the transplantation of insulin producing cells into a patient suffering from insulin dependent diabetes melitis (IDDM), wherein the cells (islets) so transplanted have been modified by irreversible adsorption with heparin or fraction or derivative thereof onto the surfaces of the individually isolated islets. This coating takes place from an aqueous solution of the heparin, e.g., Corline Heparin Conjugate, with the result of obviating the significant problem of clotting.

As pointed out in the second paragraph on page 1 of Appellants' specification, transplantation of isolated islets has proven to be considerably less successful compared to whole pancreas transplantation, and yet "there is no obvious immunological explanation as to why transplantation of whole pancreas is more successful than islet transplantation."

As pointed out in the bottom paragraph on page 2 of Appellants' specification, the present invention is based on experiments performed by the Appellants' "implying adding human, adult porcine or fetal porcine islets to human whole blood" and being "struck by the vigorous coagulation occurring when these islets were injected into human ABO-compatible blood." Based on their microscopical examinations, it became evident to them "that the islets are rapidly coated by a layer of platelets which soon develops into an organized thrombus." This biological event has previously not been considered and is now suggested to be a major explanation as to why the outcome of autologous islet transplantation has been comparatively unsuccessful." The present invention is based on this discovery.

The §102 rejection based on Nomura is unjustified.

The third declaration of Rolf Larsson, Ph.D., one of the co-inventors of the present invention, which Declaration was executed November 29, 2007, and filed with the reply of December 10, 2007, states in paragraph (14) on page 5 as follows:

> (14) Newly relied upon Nomura...discloses only the use of heparin administered systemically. Systemic administration of heparin is likely to generate bleeding complications, and has nothing to do with our invention which relates to the use of surface-bound heparin which acts locally on the surface of the islets thus eliminating bleeding complications.

Applicants' claims do not recite administering heparin. Instead, the heparin used in the present invention has been applied to the individual islets, and it is these surface-treated islets which are administered to the patient. The rejection should be withdrawn.

The §102 rejection based on Wagner is unsupportable.

At most, what Wagner discloses is an encapsulation of islets with an insoluble polymer shell, e.g., polyamide, polyester, polyolefin, etc., namely an insoluble barrier,

something quite contrary to the present invention where the heparin material is adsorbed onto the cell surface with no formation of a barrier shell. Indeed, one end of the molecule is adsorbed onto the cell surface, and the other end protrudes out from the cell. Such molecules, e.g. heparin and Corline Heparin Conjugate, are water soluble molecules. The so treated islets do not delay insulin response by the cell, because there is no membrane barrier that has to be penetrated by glucose and insulin, as inevitably must occur in the prior art, including Wagner. Further in this regard, and in support of Appellants' position, attention is invited to page 3 of the Declaration of Dr. James Shapiro, executed December 8, 2007, and filed with the reply of December 10, 2007.

The present invention differs fundamentally from Wagner in not providing an impenetrable shell around the islets.

The examiner relies on claim 8 of Wagner, but claim 8 does not disclose the use of heparin or anything similar to heparin. Please see paragraph 8 of the third Declaration of Professor Larsson. Claim 7 of Wagner does mention heparin "used to antagonize agglomeration.", but Wagner does not describe how heparin might be used in the Wagner system; please see paragraph (9) of Professor Larsson's third Declaration.

As Dr. Larsson pointed out during the interview of June 28, 2007, the examiner's interpretation of Wagner makes no sense, because, if cells of Wagner were first mixed with an anticoagulant and then encapsulated as proposed by the examiner at page 4 of the Official Action of August 9, 2007, the anticoagulant could not function because the anticoagulant would then be sealed within the microcapsule. This is confirmed as fact in paragraph 11 of the Third Declaration of Professor Larsson.

As to the fundamental difference between encapsulation (the prior art) and coating, please also see the first Declaration of Drs. Korsgren, Nilsson and Larsson executed

in February of 2004 and filed with a "Second Preliminary Amendment for Continued Examination" filed March 2, 2004; and the second Declaration of Drs. Korsgren, Nilsson and Larsson, filed with the reply of April 4, 2007.

There is no basis for the rejection based on Wagner, and such rejection should be withdrawn.

The §102 rejection based on Soon-Shiong is faulty for the same reasons as the rejection based on Wagner.

Soon-Shiong, like Wagner, does not disclose a method as called for in claims 4 and 27 "wherein said individual isolated islets are modified by an irreversible adsorption with a clotting inhibiting agent comprising heparin or a fraction or derivative thereof". There is nothing in either Wagner or Soon-Shiong which has anything to do with irreversible adsorption. This feature is neither disclosed in the references nor is it inherent in the references, as is further made clear in the second declaration of the inventors. Again, please also see page 3 of Dr. Shapiro's Declaration, and also paragraphs (12) and (13) on pages 4 and 5 of Professor Larsson's third Declaration, as well as the first and second Declarations of the inventors.

It is fundamental that the Declarations are evidence, not arguments. What is stated as fact must be accepted, and what is set forth as expert opinion must also be accepted, in the absence of evidence to the contrary, of which there is none.

Soon-Shiong does not anticipate Applicants' claims, and the rejection should be withdrawn.

The rejection based on §103 is also unsupportable.

The rejection of claim 9 under §103 is based on the validity or propriety of the rejections under §102 based on Wagner and Soon-Shiong. Couser, applied as a secondary

reference, has not been cited to make up for the aforementioned deficiencies of Wagner and Soon-Shiong, and does not do so.

Moreover, Couser is fundamentally contrary to the present invention as stated **as fact** in paragraph 15 of the third Declaration of Professor Larsson. Couser clearly relates to the systemic administration of a drug, and not to any transplantation of insulin producing cells which have already been modified as recited in claim 4, together with the added subject matter of the dependant portion of claim 9.

Claim 9 defines non-obvious subject matter, and the rejection should be withdrawn.

Respectfully submitted,
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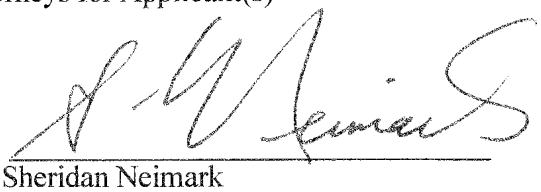
Attorneys for Applicant(s)

By: 
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